The Relationship Between Anti-Müllerian Hormone in Women Receiving Fertility Assessments and Age at Menopause in Subfertile Women: Evidence From Large Population Studies

M. Dólleman,* M. J. Faddy, J. van Disseldorp, Y. T. van der Schouw, C. M. Messow, B. Leader, P. H. M. Peeters, A. McConnachie, S. M. Nelson, and F. J. M. Broekmans

Department of Reproductive Medicine and Gynaecology (M.D., J.v.D., F.J.M.B.), Julius Center for Health Sciences and Primary Care (M.D., Y.T.v.d.S., P.H.M.P.), University Medical Centre Utrecht, 3508 GA Utrecht, The Netherlands; School of Mathematical Sciences (M.J.F.), Queensland University of Technology, 4001 Brisbane, Australia; School of Medicine (S.M.N.), University of Glasgow, Western Infirmary, Glasgow G12 8QQ, United Kingdom; Clinical Research Division, ReproSource (B.L.), Inc, Woburn, Massachusetts 01801; and Robertson Centre for Biostatistics (C.M.M., A.M.), University of Glasgow, Glasgow G12 8QQ, United Kingdom

Context: Anti-Müllerian hormone (AMH) concentration reflects ovarian aging and is argued to be a useful predictor of age at menopause (AMP). It is hypothesized that AMH falling below a critical threshold corresponds to follicle depletion, which results in menopause. With this threshold, theoretical predictions of AMP can be made. Comparisons of such predictions with observed AMP from population studies support the role for AMH as a forecaster of menopause.

Objective: The objective of the study was to investigate whether previous relationships between AMH and AMP are valid using a much larger data set.

Setting: AMH was measured in 27 563 women attending fertility clinics.

Study Design: From these data a model of age-related AMH change was constructed using a robust regression analysis. Data on AMP from subfertile women were obtained from the population-based Prospect-European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC) cohort (n = 2249). By constructing a probability distribution of age at which AMH falls below a critical threshold and fitting this to Prospect-EPIC menopausal age data using maximum likelihood, such a threshold was estimated.

Main Outcome: The main outcome was conformity between observed and predicted AMP.

Results: To get a distribution of AMH-predicted AMP that fit the Prospect-EPIC data, we found the critical AMH threshold should vary among women in such a way that women with low age-specific AMH would have lower thresholds, whereas women with high age-specific AMH would have higher thresholds (mean 0.075 ng/mL; interquartile range 0.038–0.15 ng/mL). Such a varying AMH threshold for menopause is a novel and biologically plausible finding. AMH became undetectable ($<$0.2 ng/mL) approximately 5 years before the occurrence of menopause, in line with a previous report.

Conclusions: The conformity of the observed and predicted distributions of AMP supports the hypothesis that declining population averages of AMH are associated with menopause, making AMH an excellent candidate biomarker for AMP prediction. Further research will help establish the accuracy of AMH levels to predict AMP within individuals. **(*J Clin Endocrinol Metab* 98: 1946–1953, 2013)**

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Abbreviations: AMH, anti-Müllerian hormone; AMP, age at menopause; CI, confidence interval; CV, coefficient of variation; GCRM, Glasgow Centre for Reproductive Medicine; GRI, Glasgow Royal Infirmary; Prospect-EPIC, Prospect-European Prospective Investigation into Cancer and Nutrition.

Female reproductive success and the length of a woman's fertile life span are considered to be manifestations of the dynamic decline of the primordial follicle pool. Although age is considered to be the key determinant of this decline, in young women it is not a reliable predictor of the duration of their reproductive life span, with future menopausal age potentially varying considerably between women of the same age (1). Therefore, an ever-growing body of research has aimed to identify biomarkers that adequately assess the remaining supply of follicles in the ovaries. Anti-Müllerian hormone (AMH) is such a quantitative marker of ovarian reserve. AMH is secreted by the cohort of antral follicles up to 8 mm in size (2, 3) and has been shown to adequately reflect the gradual decline in follicle numbers associated with increasing age (4). Because the onset of menopause is triggered by exhaustion of the follicle pool and considering that AMH is a reflection of the size of the remaining follicle pool, AMH has been used to predict the age at which a woman will become postmenopausal in both retrospective and prospective cohort studies (5–8). Although the predictive capacity of AMH in these studies was promising, they were based on small numbers of women, justifying further confirmation in larger cohorts.

Several models have been suggested to represent the age-related AMH decline and the age at which menopause occurs (7, 9, 10). Of these, a quadratic regression function of age has emerged as the preferred model (10, 11). However, new insights into the nature of AMH decline, such as the suggestion that AMH becomes undetectable 5 years prior to the final menstrual period (12), have prompted a collaboration of efforts to reassess the relationship between AMH and the onset of menopause, using a previously described approach (7) but with data from a vastly larger cohort of women. The aim of the current study was thus to model age at menopause based on ovarian reserve status derived from age and AMH and to confirm the conformity of predicted and observed AMP distributions.

Materials and Methods

Subjects

To investigate age-dependent changes in AMH, we combined information from different sources into 1 data set for analysis. AMH and age were obtained from women attending 3 centralized AMH testing facilities within the United Kingdom and 1 in the United States. The UK laboratories were the University of Glasgow (n = 1407) the Glasgow Centre for Reproductive Medicine (GCRM; n = 1515), and the Glasgow Royal Infirmary (GRI; n = 6783). These AMH values were measured as part of the routine fertility work-up and thus represent all women who would attend these infertility clinics. An additional group of women with normal pelvic ultrasounds and confirmed ovulation but whose partners were known to have severe male factor infertility (<5 000 000 sperm/mL) requiring intracytoplasmic sperm injection was also included (GRI, n = 927) (10). A final set of 16 931 AMH measurements was from ReproSource, a clinical reference laboratory that provides centralized AMH testing for US fertility clinics (11). For all women, samples were measured between July 2006 and October 2009. Due to the centralized sources of the AMH values, only age and AMH concentration were known, with no clinical characteristics of the women available.

The distribution of age at menopause was estimated from another cohort of women from the Prospect-European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC). This cohort consists of 17 357 women aged between 50 and 70 years who were recruited between 1993 and 1997 for a nationwide breast cancer screening program conducted in The Netherlands. Menopausal status and past reproductive health were derived from extensive questionnaires on reproductive history (13, 14). The World Health Organization definition of menopause, namely the absence of spontaneous menstrual bleeding for more than 12 months, was used. For the current study, a cross-sectional cohort of women with a recorded natural menopause was selected from the initial prospective cohort. Only women aged 58 years and older were selected to avoid underrepresentation of women who reached menopause at a late age, and from these women, only those women with some indication of subfertility provided data on age at menopause. These women were considered to be more similar (in all parameters except age) to those from whom the AMH concentrations were obtained. Subfertility was assessed via questionnaires and women were considered to have an indication of subfertility if they had 1 or more of the following criteria: (1) having had an irregular menstrual cycle pattern between 30 and 40 years of age, (2) having consulted a physician for fertility problems, (3) nulliparity, (4) uniparity, (5) having had a miscarriage, or (6) having a long time interval between the birth of the first and second child (15). After application of these selection criteria, 2249 postmenopausal women could be included in this study.

AMH assay

All four centralized AMH testing facilities used the ELISA provided by Diagnostic Systems Laboratories (Webster, Texas) to measure AMH concentrations in batches. Values were delivered in concentrations of picomoles per liter (conversion factor to picomoles per liter = nanograms per milliliter × 7.143). At the University of Glasgow laboratory, the intraassay and interassay coefficients of variation (CVs) were 6.3% and 11.4%, respectively; at the GCRM laboratory, the CVs were 3.4% and 8.6%, respectively; at the GRI laboratory, the CVs were 8.6% and 15.4%, respectively; and at the ReproSource laboratory the CVs were 5% and 8%, respectively (10, 11). The limit of detection of these AMH assays was set at 0.2 ng/mL (16).

Analysis

Modeling of age-related AMH decline

The data on AMH and age from the 4 different centers were analyzed using a robust regression methodology, with quadratic functions of age to describe the means (10, 11) and skew-*t* distributions to describe the residual variation about these means (17). [For maximum likelihood estimation (see below), those

results less than the assay detection limit contribute the information AMH < 0.2 ng/mL to the likelihood.] A natural logarithmic transformation of AMH was applied to stabilize the residual variance in AMH concentrations, thereby creating a more homogenous distribution, but the residual standard deviation was allowed to be age dependent as a check on the efficacy of this transformation. All these assumptions formed a model for age-related change in AMH concentrations with 3 components: 1) mean of log(AMH) = $\alpha + \beta \times$ age + $\gamma \times$ age^2; 2) SD of log(AMH) = exp($\sigma + \tau \times$ age); and 3) skew-*t* distribution of residuals [log(AMH) − mean]/SD.

Predicted and observed age at menopause

Our hypothesis was that variation in age-specific AMH concentrations corresponds to variation in the age at which menopause occurs, through the notion of a critical threshold whereby AMH falling below this threshold represents follicle depletion to the extent that cycles are no longer sustained and menopause follows. From the above (regression based) model for age-related change in AMH, probabilities of AMH at any specified age being below such a threshold can be calculated and related to age at menopause through the following equation: probability that AMH level at age *y* is below threshold = probability that menopause has occurred before or at age *y*.

In this way a probability distribution of age at menopause can be determined for any given threshold and thus provides a model for predicting age at menopause. Recent studies have shown substantial inter- and intracycle fluctuations in AMH for individual women (18–20), which may be affecting the AMH data but could not be expected to contribute to varying fertility between women. So to allow for such extraneous variation in AMH, a different SD and skew-*t* residual distribution from those in the regression model were used in constructing this predictive distribution of menopausal age [ie, only the equation for the mean of log(AMH) from the regression analysis was used here].

These two linked models, for AMH and age at menopause, were fitted to both data sets (AMH and Prospect-EPIC) by maximizing the combined likelihood of all these data. This approach gave estimates of all parameters used in the model to describe the following: the mean (α, β, and γ); SD (σ and τ); the skew-*t* residual distribution for the AMH and age regression model (above); the critical AMH threshold; and the (different) SD and skew-*t* residual distribution used in the construction of the predictive distribution of menopausal ages. Agreement between the AMH-based predictive distribution and the observed distribution of age at menopause was assessed by a visual comparison of their cumulative frequencies.

Nomogram

A nomogram was created to show estimated age-specific percentiles for AMH (lower 5%, 10%, and 25%; median; and upper 75%, 90%, and 95%) from the fitted (regression) model for age-related change in AMH, with the corresponding percentiles of the fitted distribution of menopausal age derived from the AMH threshold modeling. Individual predictions can be made from percentiles of the menopausal age distribution corresponding to those in which an individual woman's AMH concentration and age are located in the nomogram. Only women between the ages of 25 and 55 years are represented in the nomogram; this age range was chosen because it represents the most clinically relevant group for the prediction of the remaining fertile life. Moreover, previous studies have shown age-based AMH models to function poorly at the extremes of the age distribution (7, 10, 11).

Finally, the estimated distribution of the age at which AMH drops below the detectable limit of the AMH assay (0.2 ng/mL) was compared with the estimated distribution of the age at which AMH drops below the critical menopausal threshold to assess the time span between AMH becoming undetectable and the predicted onset of menopause.

All data were analyzed using MATLAB, version 7.2 software (The MathWorks Inc, Natick, Massachusetts).

Results and Discussion

Results

In the full AMH data set, there were 3394 women with AMH values less than 0.2 ng/mL and actual values from 24 169 women. This latter group had a mean age of 34.6 years (±5.3 years) and mean AMH of 2.5 ng/mL (±2.8 ng/mL). In the cohort of the women with any indication of subfertility in the Prospect-EPIC data set (n = 2249), the mean age was 63.3 years (±3.4 years), with a mean age at the natural menopause of 49.9 years (±4.5 years) and a median 50 years. Table 1 provides the summary statistics of the different cohorts of subjects.

The mean age-related AMH profiles from individual regression analyses of data from the 4 different sources are shown in Supplemental Figure 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. The fitted quadratic regressions of log(AMH) on age from the different centers are very similar, particularly over the age range of 25–55 years, although

Table 1. Summary Statistics of the Different Cohorts of Subjects

	GRI	GCRM	UoG	US	Prospect-EPIC
n	7710	1515	1407	16 931	2249
Age, y	34.0 (30.0–38.0)	36.8 (32.9–39.8)	34.9 (31.4–37.5)	35.3 (31.0–39.0)	63.0 (60.0–66.0)
AMH, ng/mL	2.07 (0.97–3.74)	1.43 (0.74–2.77)	1.67 (0.80–2.95)	1.60 (0.76–3.15)	
AMH measures below detection, n	729	196	134	2335	
Age at menopause, y					50.0 (48.0–53.0)

Abbreviations: UoG, University of Glasgow; US, ReproSource United States. Data are medians (interquartile range) unless otherwise indicated.

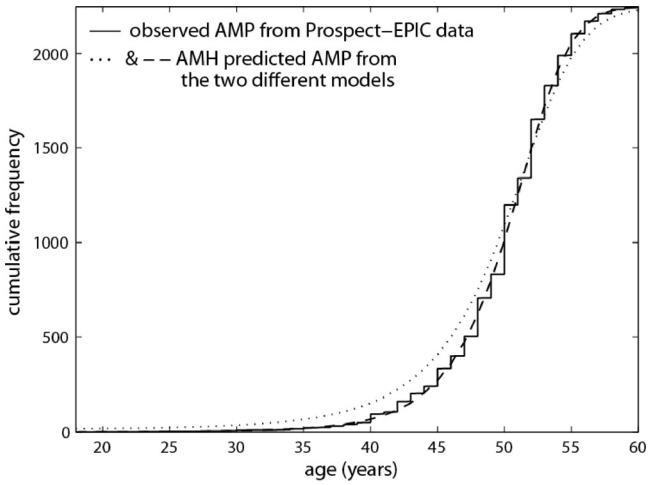

Figure 1. Predicted vs observed distributions of age at menopause. The distribution of observed AMP from the Prospect-EPIC cohort of subfertile women (solid line) is shown compared with 2 predictive distributions constructed from AMH falling below a critical threshold; the dotted line shows relatively poor agreement when the residual distribution of AMH from the regression analysis is used in the predictive model for AMP, whereas the dashed line shows much better agreement from using a different distribution of AMH.

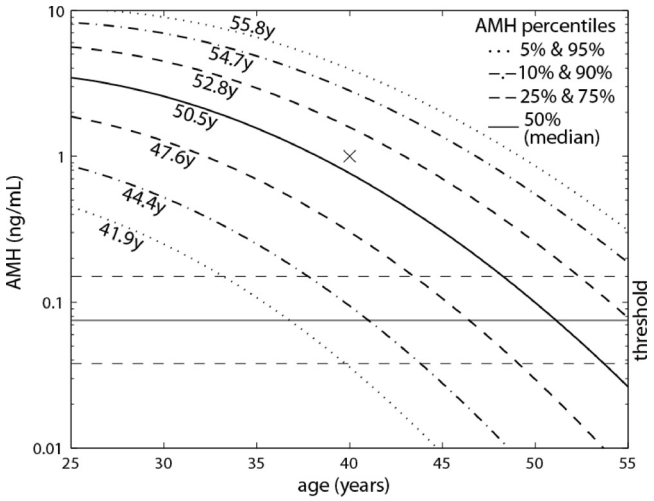

Figure 2. AMH nomogram and predictions of age at menopause. The estimated age-specific 5%, 10%, 25%, 50%, 75%, 90%, and 95% AMH percentiles from the fitted regression model are plotted. The corresponding percentiles of AMP modeled by AMH falling below a critical threshold are shown adjacent to these AMH percentiles. The critical threshold (0.075 ng/mL) is depicted by the faint solid horizontal line, whereas the faint dashed horizontal lines indicate the approximate interquartile range when the threshold is allowed to vary. A 40-year-old female with an AMH of 1 ng/mL, which is between the 50th and 75th percentiles (denoted by ×) would thus be expected to have an AMP between 50.5 and 52.8 years.

the differences between these profiles were statistically significant ($P < .001$) due to the large amount of data used. At the extremes of age, greater discrepancies were apparent, but this can be largely accounted for by the estimated means being less precise there. Moreover, only 0.3% of the residual SD could be attributed to the differences between the sources, so these differences were deemed to be of no practical or clinical significance. There is a clear trend of decreasing AMH with increasing age after about 25 years in all the profiles.

The mean age-related AMH profile from a single regression analysis of the combined data from all 4 sources plotted with the corresponding 95% confidence intervals (CIs) and the 90% probability range for observed AMH values are shown in Supplemental Figure 2. According to this figure, the mean AMH starts to decline from approximately 20 years of age and continues to decline steadily until it becomes undetectable. The logarithmic transformation of AMH has slightly overcompensated for the heterogeneous residual variation of the raw AMH data as can be seen from the broadening 90% probability range with increasing age.

Figure 1 shows the fit of the distribution of age at menopause predicted by AMH falling below a critical threshold estimated to be 0.075 ng/mL (with SE 0.004), in which good agreement can be seen with the distribution from the Prospect-EPIC data on women with any indication of subfertility. Shown for comparison is the very poor fit obtained by assuming the same distribution of log(AMH) in constructing the predictive distribution of menopausal ages as that from the regression analysis of log(AMH) and age. In fact, the residual SD from this regression analysis had to be reduced by multiplying it by an estimated factor of 0.56 (95% CI 0.51–0.61) to achieve the improved fit shown in Figure 1; in other words, there was significantly ($P < .001$) more variation in the AMH levels than would be needed to explain the variation in age at menopause. All of the model parameter estimates are shown in the online Supplemental Table 1.

In Figure 2, a nomogram is depicted that describes an age-related AMH decline for women in terms of the fifth, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of age-specific AMH concentrations. The estimated critical AMH threshold (0.075 ng/mL) is also indicated in this figure. The corresponding percentiles of the predictive distribution of age at menopause (AMP) are shown adjacent to these AMH percentile curves in Figure 2; the estimated fifth, 10th, and 25th AMP percentiles (with SEs in parentheses) are 41.9 (0.27) years, 44.4 (0.19) years, and 47.6 (0.12) years, respectively; the estimated 50th AMP percentile (or median) is 50.5 (0.09) years, and estimated 75th, 90th, and 95th AMP percentiles are 52.8 (0.08) years, 54.7 (0.10) years, and 55.8 (0.11) years, respectively. Women with AMH concentrations between percentiles can expect menopause to occur between the corresponding AMP percentiles; for example, a 40-year-old woman with an AMH concentration of 1 ng/mL, which is just above the 50th AMH percentile and just below the

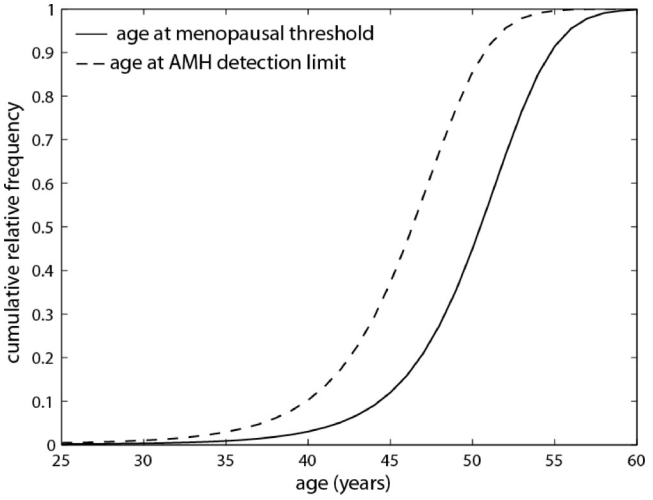

Figure 3. Comparison of the distributions of age at which the AMH threshold and AMH assay detection limit are reached. The estimated distribution of the age at which AMH drops below the detection limit (dashed line) showing that this occurs about 5 years before AMH drops below the critical threshold for menopause (solid line).

75th percentile (denoted by × in Figure 2), can expect menopause just after 50.5 years and below 52.8 years.

Figure 3 shows that the age at which a woman's AMH drops below the detection limit of the assay that was used in this study (0.2 ng/mL) has a distribution that, when compared with the distribution of the age at which AMH falls below the critical threshold for menopause, indicates that menopause occurs approximately 5 years after AMH becomes undetectable.

Discussion

This study demonstrates 2 important things. First, we have shown a close conformity between the distribution of observed age at menopause and a predictive distribution using a robust regression model of changing AMH with increasing age and the assumption that menopause is associated with AMH falling below a critical threshold (in which AMH represents follicle depletion to the extent to which menopause ensues). Second, we have confirmed earlier reports that AMH becomes undetectable approximately 5 years prior to menopause. The close conformity of the shape of the observed and AMH-predicted distributions of age at menopause supports the hypothesis that AMH influences the timing of reproductive milestones such as menopause. The findings in this study generally confirm both the dynamics of age-related AMH decline as well as the possibility of prediction of age at menopause as demonstrated in previous studies (7, 10, 11). Both findings will have impact on research lines in which prospective data are now being obtained to demonstrate the claim that AMH at a young age could be a forecaster of reproductive life span.

The estimated AMH threshold after which menopause occurs was 0.075 ng/mL, slightly lower than the value (0.086 ng/mL) given by van Disseldorp et al in 2008 (7), which was based on a much smaller data set of proven fertile women with only a fraction (~0.5%) of the AMH values used in this study and is consequently a much less precise estimate, and in any case different menopausal age data were used. Unfortunately, it would not be possible to confirm this threshold in any prospective study because the AMH assay applied in this study is not considered to be accurate below a detection limit of 0.2 ng/mL (16, 21, 22). Nevertheless, because it is not uncommon to find 1 or 2 antral follicles by ultrasound in postmenopausal women, this threshold seems plausible.

The finding from our modeling, that the age at which AMH falls below the critical threshold for menopause tends to be about 5 years after the age at which AMH drops below the detection limit of the assay, is in concordance with Sowers et al (12), who showed that AMH values decline to or past the detection limit at approximately 5 years before the final menstrual period.

In achieving the good fit to the Prospect-EPIC data on menopausal ages, it was necessary to reduce the SD of log(AMH) used in constructing the AMH-based predictive distribution by multiplying the residual SD from the regression model of log(AMH) and age by an estimated 0.56 (95% CI 0.51–0.61). Some excess AMH variation will be due to the inter- and intracycle variation within women, and van Disseldorp et al (18) have shown that 11% of the (age adjusted) AMH variance could be due to the intercycle variation and 13% due to the intracycle variation for individual women. If these 2 sources of the extraneous AMH variation were independent, then 76% of the overall AMH variance (or 87% of the SD) would be due to the variation between women; but if these sources were positively correlated, then the variation between women could be as low as 52% (corresponding to maximal correlation) of the overall AMH variance (or 72% of the SD). This figure of 0.72 is outside the above 95% CI for the estimated factor by which the AMH residual SD was reduced to achieve a good fit of the predictive distribution of menopausal age. This means that the inter- and intracycle AMH variation within women cannot explain all of the excess variation in AMH apparent from the regression analysis, and a significant amount remains.

The effect of any excess AMH variation can be reduced by allowing the critical AMH threshold for menopause to vary between women in such a way that it is positively correlated with their actual AMH concentration: higher for women with high AMH for their age and lower for

women with low AMH for their age, thereby reducing the variation of the AMH-predicted age at menopause. Using the above figure of 72% of the AMH residual SD in the determination of the predicted distribution of menopausal ages leads to an approximate estimate of the interquartile range of the necessary threshold variation of 0.038–0.15 ng/mL. This is indicated in Figure 2 with the previous (constant) threshold estimate (0.075 ng/mL) now being the mean. Thresholds within this interquartile range would be more likely for women with AMH concentrations between the corresponding (25th and 75th) AMH percentiles than for women with AMH outside these percentiles who would be more likely to have more extreme threshold values.

This discrepancy between variation in age at menopause and residual variation in AMH may not be an artifact of AMH, for a similar discrepancy between variation in age at menopause and residual variation in nongrowing follicles is apparent in the study by Wallace and Kelsey (23) in which the menopausal age prediction was based on follicle numbers falling below a critical level of 1000: in that study the 95% prediction interval was 39–60 years compared with the observed 40–57 years from the Prospect-EPIC data from women with and without any indication of subfertility. Perhaps it can be reasoned as follows: if women with a higher-than-average AMH for their age are predestined to have a higher age at menopause, then this would result in an increased time frame for other determinants of the ovarian aging process to play a role, thus resulting in menopause occurring despite still having some follicles left in the ovaries. The supposed determinants may be somatic or ovarian factors that prevent ovulation and cycling at near, but not complete, depletion of the follicle pool. Alternatively, a compensatory mechanism may exist whereby prematurely aged ovaries (as expressed by lower than average age specific AMH levels) have a decreased threshold for menopause as a means of extending reproductive life. Evidence for such a varying threshold can be gleaned from recent studies in which data show that some women are regularly cycling despite their AMH concentrations being clearly below the detection limit and very close to zero (19, 24). Furthermore, a study in 50 postmenopausal women revealed that 36% of women still had an AMH above the assay's limit of detection at their final menstrual period, whereas 64% were below it (12).

There also may be other sources of extraneous AMH variation that could reduce the need for a varying threshold. Some extraneous AMH variation in this study would be from the different sources of the data, but this only amounted to a negligible 0.3% of the residual SD. It could be argued that the excess variation in AMH may be explained simply by characteristics of the cohort. Because the AMH values are measured in women attending an infertility clinic, one can expect the cohort to include women with either polycystic ovary syndrome (high age specific AMH) or premature ovarian insufficiency (low age specific AMH), which could contribute to excess variation in AMH (25, 26). Extra variation in AMH may be due to lifestyle factors like smoking, which has been associated with a decrease in age-specific AMH and an earlier age at menopause (27–29). Assuming similarity between the AMH cohort and the Prospect-EPIC cohort, it is, however, likely that the level of occurrence of such determinants of AMH would also be similar, and hence, their effects on AMH-predicted age at menopause might be expected to be similar.

The major strength of this study is that it provides the largest body of information in which the association between AMH and age at menopause has ever been tested. There are, however, some limitations; for example, data on age at menopause were based on self-reporting, which may be prone to recall bias. However, several studies have demonstrated that both the validity and reproducibility of self-reported age at menopause are good (30, 31). And from the cohorts of women from whom AMH was measured, only age and AMH is known; other determinants of age at menopause such as genetic factors, lifestyle factors, and reproductive history could not be compared between this sample of women and the Prospect-EPIC sample (32). A varying AMH threshold might be seen as a bit of a drawback in the model for age at menopause in that although it results in a better-fitting model, it cannot be known with any certainty for an individual at what threshold AMH would be predictive of menopause. Some uncertainty in predictions is already apparent according to a prospective study that showed large and overlapping 95% confidence intervals for the predicted ages at menopause (5).

Although the findings of the current study support the notion that AMH does reflect female reproductive status, applying this to get clinically useful information for individual women remains problematic. First, the AMH assay is no longer widely used because it has been replaced by a newer AMH GEN II assay (Beckman Coulter, Sinsheim, Germany). AMH concentrations measured with the GEN II assay give higher values than the ELISA used in this study (10, 11). Although consistent correlations have been found between the newer AMH GEN II assay and the Diagnostic Systems Laboratory assay (21, 33), the results shown here should be interpreted as conceptual evidence that prediction of age at menopause from declining AMH is possible, rather than used for counseling of individual patients. Further research on the relationship between

AMH and age at menopause would benefit from using the newer assay.

Using average AMH concentrations over several cycles and phases of these cycles would reduce the effect of natural fluctuations between and within cycles; for example, averaging 4 measurements could reduce the SD of these effects by 50%. Additional evidence still needs to be obtained from long-term follow-up studies in which the occurrence of menopause is prospectively assessed and women are subjected to multiple measurements of AMH over several cycles spaced over a period of 1 or 2 decades. Four prospective studies exist that provide evidence that AMH can be used to make more individualized predictions of age at menopause. However, either the follow-up time was not very long, resulting in few women reaching menopause, or the included women were of late reproductive age when the AMH was determined. Furthermore, in 3 of the studies, AMH was measured only once, thus not permitting the analysis of natural variation within the individual (5, 6, 8). In the other study, the prediction was based on estimating the rate of change in AMH, but it took 3.5 years to get a reliable estimate, and thus 3.5 years before a prediction could be made (6).

Menopause is the only noticeable marking point for the massive, gradual decline in ovarian follicle numbers over the first 5 decades of a female's life. It can be seen as the end of the reproductive life span in women. Age at menopause shows considerable variation between 40 and 60 years, with approximately 10% of women becoming menopausal before the age of 45 years. A relationship between age at menopause and the end of natural fertility is thought to be present, with an interval of approximately 10 years (34). Therefore, from the prediction of age at menopause, similar predictions of age at the end of natural fertility can be extrapolated.

In conclusion, this study shows that AMH levels have an association with reproductive events such as age at menopause and reinforces the notion that AMH is capable of predicting the timing of such events more informatively than chronological age alone.

Acknowledgments

Address all correspondence and requests for reprints to: M. Dólleman, MD, University Medical Center Utrecht, Room 05.126, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: m.dolleman-2@umcutrecht.nl.

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